

REMARKS UNDER 37 CFR §1.116

Applicants acknowledge the current status of the claims as reported in the Office Action mailed 11 April 2006. Claims 5-12 and 14-61 are currently pending in this application, claims 37 and 38 are allowable, claims 39-43 and 47-60 are withdrawn from consideration, and claims 5-12, 14-38, 44-46 and 61 are under consideration. Reconsideration and allowance of the application in light of the foregoing amendments and the following remarks are respectfully requested.

Claims 22, 29 and 36 are amended by replacing the term "-- at least two variable regions --" with the terms "-- one heavy chain variable region and one light chain variable region --", such that the claimed antibody, or antigen binding fragment thereof, comprises one heavy chain variable region and one light chain variable region. Support for these amendments can be found throughout the specification as filed, and particularly at pages 11-12. No new matter is added. These amendments are made without prejudice, solely to advance examination of the present application to allowance. Applicants reserve the right to prosecute original subject matter in a later-filed continuation application, which properly claims the benefit of this application.

Reconsideration and allowance of the pending claims in light of the foregoing amendments and the following remarks are respectfully requested.

**Claim rejections under 35 USC §112 first paragraph**

In the Office Action, at page 2, claims 22, 29, 36 and their dependent claims 23-28, 32-35 and 44-46 are rejected under 35 USC §112, first paragraph, as containing subject matter not described in such a way as to convey to one skilled in the art that the Applicant was in possession of the claimed invention. Specifically, the Examiner asserts that Applicants have disclosed single chain antibodies comprising one variable region from light chain and one variable region from heavy chain but have not disclosed antibodies which comprise two heavy or two light chain variable regions. Applicants respectfully disagree, and traverse the rejection for reasons of record set forth in responses to previous office actions.

Notwithstanding Applicants' traverse, for purposes of advancing examination of the present application to allowance only, Applicants have amended claims 22, 29 and 36 by replacing the term "-- at least two variable regions --" with the terms "-- one heavy chain variable region and one light chain variable region --", such that the claimed antibody, or antigen binding fragment thereof, comprises one heavy chain variable region and one light chain variable region. Support for these amendments can be found throughout the specification as filed, and particularly at pages 11-12 and in Examples 2. No new

matter is added. Applicants reserve the right to prosecute the original subject matter in a later-filed continuation application, which properly claims the benefit of this application.

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 22, 29, 36 and their dependent claims 23-28, 32-35 and 44-46 under 35 USC §112 first paragraph.

In the Office Action, at page 4, claims 22-36 and claims 44-46 remain rejected under 35 USC §112, first paragraph, as containing subject matter not described in such a way as to convey to one skilled in the art that the Applicant was in possession of the claimed invention. Specifically, the Examiner continues to assert that the specification, while disclosing antibodies and antigen-binding fragments thereof, in which the three CDR's in the heavy chain variable region or the three CDR's in the light chain variable region are all defined by a single antibody, and which bind the relevant antigen (human IL-18 or a peptide epitope thereof), and for mutants of these antibodies in which a limited number of defined changes are made in one or more CDRs; does not reasonably provide written description for antibodies and antigen-binding fragments thereof that comprise less than three heavy chain CDRs or three light chain CDRs defined by the amino acid sequence of a parental antibody that binds the same antigen. Specifically, the Examiner continues to point to claims 30 and 31 which recite a light chain variable region having an amino acid sequence of SEQ ID No:15 and asserts that the specific sequence represents only a small portion, but not three CDR's of a light chain. Applicants respectfully disagree, and traverse the rejection for reasons set forth in responses to previous office actions.

Notwithstanding Applicants' traverse, for purposes of advancing examination of the present application to allowance only, Applicants have amended claims 22, 29 and 36 by replacing the term "-- at least two variable regions --" with the terms "-- one heavy chain variable region and one light chain variable region --", such that the claimed antibody comprises one heavy chain variable region and one light chain variable region. Support for these amendments can be found throughout the specification as filed, and particularly at pages 11-12 and in Examples 2. No new matter is added. Applicants reserve the right to prosecute the original subject matter in a later-filed continuation application, which properly claims the benefit of this application.

In view of the foregoing amendments and remarks, Applicants respectfully request the removal of the rejection of claims 22-36 and 44-46 under 35 USC §112, first paragraph.

In the Office Action, at page 5, claims 22-36 and claims 44-46 remain rejected under 35 USC §112, first paragraph, as containing subject matter not described in such a way as to convey to one skilled in the art that the Applicant was in possession of the claimed invention. Specifically, the Examiner

asserts that the specification while being enabling for antibodies and antigen binding fragments thereof comprising one variable region from L chain, and one variable region from H chain, does not reasonably provide enablement for antibodies and antigen binding fragments thereof where both variable regions are from L chain or a H chain. Applicants respectfully disagree, and traverse the rejection for reasons set forth in responses to previous office actions.

Notwithstanding Applicants' traverse, for purposes of advancing examination of the present application to allowance only, Applicant has amended claims 22, 29 and 36 by replacing the term "-- at least two variable regions --" with the terms "-- one heavy chain variable region and one light chain variable region --", such that the claimed antibody comprises one heavy chain variable region and one light chain variable region. Support for these amendments can be found throughout the specification as filed, and particularly at pages 11-12 and in Examples 2. No new matter is added. Applicants reserve the right to prosecute the original subject matter in a later-filed continuation application, which properly claims the benefit of this application.

In view of the foregoing amendments and remarks, Applicants respectfully request the removal of the rejection of claims 22-36 and 44-46 under 35 USC §112, first paragraph.

**Claim rejections under 35 USC §103(a)**

In the Office Action, at page 5, claims 5-12, 14-24, 44-46 and 61 are again rejected under 35 USC §103(a) as being unpatentable over Kucherlapati et al., (US Patent No. 6,075,181) and Dinarello et al., (J. Leukoc. Biol. 1998; 63:658-664). Examiner continues to assert that the combination of Dinarello et al. and Kucherlapati et al. provide both the motivation to produce human antibodies to human IL-18. Applicants respectfully disagree for reasons set forth in responses to previous office actions.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all claim limitations. Second, there must be a reasonable expectation of success. Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. (see generally MPEP § 2143).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970) [MPEP §2143.03].

Hindsight reconstruction of a claimed invention, absent a teaching or suggestion in the art is impermissible. (MPEP § 2142).

Applicant's invention is directed to human antibodies or antigen binding portions thereof capable of binding human IL-18. Specifically, the claims are directed to human antibodies or antigen binding portions thereof capable of binding human IL-18 with specific binding characteristics defined by  $k_{off}$  rate constants or specific inhibitory characteristics defined by  $IC_{50}$  values.

Dinarello et al. disclose recombinant human IL-18. The cited art identifies IL-18 as a potential therapeutic target, and discloses possible “therapeutic options for specific blockade of IL-18: neutralizing anti-18 antibodies, soluble receptors to IL-18, and non-agonistic antibodies that bind either the ligand binding IL-18R or the IL-1Rrp.” Dinarello et al. do not teach, suggest or motivate one skilled in the art to generate fully human antibodies to human IL-18 with specific binding characteristics with respect to the antigen defined by  $k_{off}$  rate constants or specific inhibitory characteristics defined by  $IC_{50}$  values.

Kucherlapati et al. disclose a method of generating fully human antibodies to antigens. Kucherlapati et al. do not disclose human IL-18 as an antigen. Kucherlapati et al. do not disclose IL-18, generally, as an antigen. Finally, Kucherlapati et al. do not teach, suggest or motivate one skilled in the art to generate a fully human antibody to either IL-18, or specifically to human IL-18 with specific binding characteristics with respect to the antigen defined by  $k_{off}$  rate constants or specific inhibitory characteristics defined by  $IC_{50}$  values.

Applicants again assert that the above-cited references, either singularly or in combination, do not teach, suggest, or motivate one skilled in the art, Applicants' human anti-IL-18 antibodies or method of making the same. Neither reference teach, or suggest, all the claim limitations. The Examiner continues to assert that, “Dinarello teaches availability of human IL-18, the involvement of IL-18 in clinical pathology as that antibodies to IL-18 can inhibit the in vivo production of other pro-inflammatory cytokines, and neutralizing anti-IL-18 antibodies are a therapeutic option for specific blockade of IL-18.” Further the Examiner asserts that since Kucherlapati et al. disclose a method of generating fully human antibodies to antigens, including cytokines, it would be “instantly obvious” to one of ordinary skill in the art to combine the two references and make Applicants' fully human anti-IL-18 antibody for the purpose of treating diseases. Applicants respectfully disagree and submit that a disclosure of a method to generate human monoclonal antibodies, combined with a reference disclosing neutralizing anti-IL-18 antibodies is not a clear and particular teaching, suggestion, or motivation to one of skill in the art to make the fully human anti- IL-18 antibody of the present invention. While Dinarello et al. disclose IL-18 as a potential therapeutic target, along a “wish list” of “therapeutic options” including neutralizing antibodies, and Kucherlapati et al. disclose a method of generating fully human antibodies to antigens, the references neither singularly nor in combination teach, suggest or motivate one skilled in the art to generate fully human antibodies to human IL-18 with specific binding characteristics with respect to the antigen defined by  $k_{off}$  rate constants or specific inhibitory characteristics defined by  $IC_{50}$  values.

Therefore, the first requirement that the prior art reference (or references when combined) must teach or suggest all claim limitations is not met.

In fact, Applicants again assert that, in view of the stated potential role of IL-18 as a therapeutic target, the fact that neither reference teach or suggest a fully human anti-human IL-18 monoclonal antibody is evidence (by its absence) that such an approach is novel, unobvious, and even unobvious-to-try (even to the principal investigators of the cited art, much less a person of ordinary skill in the art) at the time of filing the present invention.

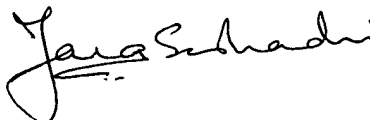
In conclusion, Applicants assert that the Examiner fails to provide the requisite "*clear and particular showing*" of any suggestion or motivation to combine the cited references. The Examiner cites In re Schulze, 145 USPQ 716, 718 (CCPA 1965) and asserts that the arguments of counsel cannot take place of objective evidence in the record. Applicants respectfully submit that there is no objective evidence in the record and the Examiner has failed to show that all the claim limitations of Applicants' invention are taught or suggested by the cited art.

In sum, the cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 4-12, 14-24, 44-46 and 61 as obvious under 35 USC §103(a). In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 5-12, 14-24, 44-46 and 61 under 35 USC §103(a).

### Conclusion

In view of the foregoing amendments and remarks, Applicants believe the rejections set forth in the Office Action dated 11 April 2006 have been avoided or overcome and consequently their application is in condition for allowance. Applicants, therefore, respectfully request reconsideration and removal of the rejections, and allowance of the pending claims as amended.

Respectfully submitted,



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